Biorheology 39 (2002) 237–246
IOS Press

(2) Osteoarthritis

The role of cytokines in osteoarthritis pathophysiology

Julio C. Fernandes *, Johanne Martel-Pelletier and Jean-Pierre Pelletier

Osteoarthritis Research Unit, Centre hospitalier de l'Université de Montréal, Hôpital Notre-Dame, Montréal, Québec, Canada

Abstract. Morphological changes observed in OA include cartilage erosion as well as a variable degree of synovial inflammation. Current research attributes these changes to a complex network of biochemical factors, including proteolytic enzymes, that lead to a breakdown of the cartilage macromolecules. Cytokines such as IL-1 and TNF-alpha produced by activated synoviocytes, mononuclear cells or by articular cartilage itself significantly up-regulate metalloproteinases (MMP) gene expression. Cytokines also blunt chondrocyte compensatory synthesis pathways required to restore the integrity of the degraded extrecellular matrix (ECM). Moreover, in OA synovium, a relative deficit in the production of natural antagonists of the IL-1 receptor (IL-1Ra) has been demonstrated, and could possibly be related to an excess production of nitric oxide in OA tissues. This, coupled with an upregulation in the receptor level, has been shown to be an additional enhancer of the catabolic effect of IL-1 in this disease.

IL-1 and TNF-α significantly up-regulate MMP-3 steady-state mRNA derived from human synovium and chondrocytes. The neutralization of IL-1 and/or TNF-α up-regulation of MMP gene expression appears to be a logical development in the potential medical therapy of OA. Indeed, recombinant IL-1receptor antagonists (ILRa) and soluble IL-1 receptor proteins have been tested in both animal models of OA for modification of OA progression. Soluble IL-1Ra suppressed MMP-3 transcription in the rabbit synovial cell line HIG-82. Experimental evidence showing that neutralizing TNF-α suppressed cartilage degradation in arthritis also support such strategy. The important role of TNF-α in OA may emerge from the fact that human articular chondrocytes from OA cartilage expressed a significantly higher number of the p55 TNF-alpha receptor which could make OA cartilage particularly susceptible to TNF-alpha degradative stimuli. In addition, OA cartilage produces more TNF-α and TNF$\angle\alpha$ convertase enzyme (TACE) mRNA than normal cartilage. By analogy, an inhibitor to the p55 TNF-α receptor may also provide a mechanism for abolishing TNF-α-induced degradation of cartilage ECM by MMPs. Since TACE is the regulator of TNF-α activity, limiting the activity of TACE might also prove efficacious in OA. IL-1 and TNF-α inhibition of chondrocyte compensatory biosynthesis pathways which further compromise cartilage repair must also be dealt with, perhaps by employing stimulatory agents such as transforming growth factor-beta or insulin-like growth factor-I.

Certain cytokines have antiinflammatory properties. Three such cytokines – IL-4, IL-10, and IL-13 – have been identified as able to modulate various inflammatory processes. Their antiinflammatory potential, however, appears to depend greatly on the target cell. Interleukin-4 (IL-4) has been tested *in vitro* in OA tissue and has been shown to suppress the synthesis of both TNF-α and IL-1β in the same manner as low-dose dexamethasone. Naturally occurring antiinflammatory cytokines such as IL-10 inhibit the synthesis of IL-1 and TNF-α and can be potential targets for therapy in OA. Augmenting inhibitor production *in situ* by gene therapy or supplementing it by injecting the recombinant protein is an attractive therapeutic target, although an *in vivo* assay in OA is not available, and its applicability has yet to be proven. Similarly, IL-13 significantly inhibits lipopolysaccharide (LPS)-induced TNF-α production by mononuclear cells from peripheral blood, but not in cells from inflamed synovial fluid. IL-13 has important biological activities: inhibition of the production of a wide range of proinflammatory cytokines in monocytes/macrophages, B cells, natural killer cells and endothelial cells, while increasing IL-1Ra production. In OA synovial membranes treated with LPS, IL-13 inhibited the synthesis of IL-1β, TNF-α and stromelysin, while increasing IL-1Ra production.

In summary, modulation of cytokines that control MMP gene up-regulation would appear to be fertile targets for drug development in the treatment of OA. Several studies illustrate the potential importance of modulating IL-1 activity as a means to reduce the progression of the structural changes in OA. In the experimental dog and rabbit models of OA, we have demonstrated that *in vivo* intraarticular injections of the IL-Ra gene can prevent the progression of structural changes in OA. Future directions in the research and treatment of osteoarthritis (OA) will be based on the emerging picture of pathophysiological events that modulate the initiation and progression of OA.

Keywords: OA, proinflammatory cytokines, antiinflammatory cytokines, cytokine antagonists

*Address for correspondence: Julio C. Fernandes, M.D., M.Sc., Associate Professor of Medicine, Hôpital Notre-Dame du Centre hospitalier de l'Université de Montréal, 1560 east rue Sherbrooke, Montréal, Québec, Canada H2L 4M1. Tel.: +1 514 890 8000, ext. 25114; E-mail: julio.fernandes@sympatico.ca.

1. Introduction

Osteoarthritis (OA) is believed to be a consequence of mechanical and biological events that destabilize the normal coupling of degradation and synthesis within articular joint tissues. In primary OA, no trauma or other predisposing factor is identified, and intrinsic alterations of the articular tissue, or response to normal cumulative stresses, are presumed responsible [43]. The disease process affects not only the articular cartilage, but also the entire joint structure including the subchondral bone, ligaments, capsule, synovial membrane and periarticular muscles. Morphological changes observed in OA include cartilage erosion as well as a variable degree of synovial inflammation. Current research attributes these changes to a complex network of biochemical factors, including proteolytic enzymes, which lead to a breakdown of the cartilage macromolecules. This disease process involves a disturbance in the normal balance of degradation and repair in articular cartilage, synovial membrane and subchondral bone [33, 37,53,62].

2. Cytokines and osteoarthritis

It is believed that cytokines and growth factors play an important role in the pathophysiology of OA. They are closely associated with functional alterations in synovium, cartilage and subchondral bone, and are produced both spontaneously and following stimulation by the joint tissue cells. Cytokines such as IL-1 and TNF-alpha produced by activated synoviocytes, mononuclear cells or by articular cartilage itself significantly up-regulate metalloproteinases (MMP) gene expression. Cytokines also blunt chondrocyte compensatory synthesis pathways required to restore the integrity of the degraded extracellular matrix (ECM). Moreover, in OA synovium, a relative deficit in the production of natural antagonists of the IL-1 receptor (IL-1Ra) has been demonstrated, and could possibly be related to an excess production of nitric oxide in OA tissues. This, coupled with an upregulation in the receptor level, has been shown to be an additional enhancer of the catabolic effect of IL-1 in this disease. In OA synovial membrane, the synovial lining cells are key inflammatory effectors. Once cartilage degradation has begun, the synovial membrane phagocytoses the breakdown products released into the synovial fluid. Consequently, the membrane becomes hypertrophic and hyperplasic. Several studies have reported inflammatory changes in the synovial membrane of patients with OA that, on occasion, were almost indistinguishable from those in patients with an inflammatory arthritis such as rheumatoid arthritis (RA) [33,37,53,62].

2.1. Proinflammatory cytokines

Proinflammatory cytokines are believed to play a pivotal role in the initiation and development of this disease process [19,68,87]. IL-1 and TNF-alpha can induce joint articular cells, such as chondrocytes and synovial cells, to produce other cytokines such as IL-8, IL-6, as well as stimulate proteases and prostaglandin E_2 (PGE_2) production. IL-1beta and TNF-alpha have also been shown to increase osteoclastic bone resorption *in vitro* [12]. Blocking IL-1 activity with the IL-1 receptor antagonist (IL-1Ra) in synovial fibroblasts *in vitro* reduced IL-6 and IL-8 production, but not TNF-alpha [34]. Moreover, adding anti-TNF-alpha antibodies to synovial cells greatly reduced the production of other proinflammatory cytokines such as IL-1, GM-CSF, IL-6 [15].

IL-1beta is primarily synthesized as a 31 kilodalton (kD) precursor and released in the active form of 17.5 kD [61,79]. In synovial membrane, synovial fluid and cartilage, IL-1beta has been found in the active form. *Ex vivo* OA synovial membrane secretes this cytokine [67]. Several serine proteases can process the

pro-IL-1beta to bioactive form [13]. In mammals only one protease, belonging to the cysteine-dependent protease family and named IL-1beta converting enzyme (ICE or Caspase-1), can specifically generate the mature 17.5 kD cytokine [13,51]. ICE is a pro-enzyme polypeptide of 45 kD [p45] located in the plasma membrane [91]. The biological activation of cells by IL-1 is mediated through association with two specific cell-surface receptors (IL-1R), named type I and type II [80]. Type I receptor binds IL-1beta more than IL-1alpha and appears responsible for signal transduction [8,59,71]. Type II IL-1R has a greater affinity for IL-1alpha than IL-1beta. The number of type I IL-1R is significantly increased in OA chondrocytes and synovial fibroblasts [59,71]. This appears to be responsible for the higher sensitivity of these cells to stimulation by IL-1 [59].

Both types of IL-1R can also be shed from the cell surface, and exist extracellularly in truncated forms; they are named IL-1 soluble receptors (IL-1sR). The shed receptor may function as a receptor antagonist because the ligand-binding region is preserved, thus enabling it to compete with the membrane-associated receptors of the target cells. Similarly, the shedding of surface receptors may decrease the responsiveness of target cells to the ligand. It is suggested that type II IL-1R serves as the main precursor for shed soluble receptors. The binding affinity of IL-1sR to both IL-1 isoforms and IL-1Ra differs. Type II IL-1sR binds IL-1beta more readily than IL-1Ra; in contrast, type I IL-1sR binds IL-1Ra with high affinity [8,29,82].

TNF-alpha appears to be an important mediator of matrix degradation and a pivotal cytokine in synovial membrane inflammation in OA, although being detected in OA articular tissue low levels. TNF-alpha is synthesized as a precursor protein comprising 76 amino acids. Proteolytic cleavage takes place at the cellular surface via a TNF-alpha converting enzyme named TACE [14]. This enzyme is also required for shedding the TNF receptors. An upregulation of TACE mRNA in human OA cartilage has recently been reported [7]. Human TNF-alpha is converted to the 157-residue (17 kD) secreted protein that oligomerizes to form trimers [3].

TNF-alpha binds to two specific receptors on the cell membrane [28,73,76]. These two TNF-R have molecular masses of 55 to 60 kD and 75 to 80 kD [54,72], and are named according to their molecular weight; TNF-R55 and TNF-R75. Their extracellular domains share 28% identity [17,45]. There is a complete absence of homology between the intracellular domains of the two TNF-R and any other known protein receptor [52,54,72,81]. In articular tissue cells, TNF-R55 seems to be the dominant receptor responsible for mediating TNF-alpha activity. In OA chondrocytes and synovial fibroblasts, enhanced expression of TNF-R55 has been reported [4,90]. Both receptor types appear to be actively involved in signal transduction [4,42,63,77,85]. Each receptor type has been shown to induce a specific subset of TNF-alpha activities [44,84]. TNF-R55 and TNF-R75 are linked to distinct intracellular second-messengers. TNF-R75 may regulate the rate of TNF-alpha association to TNF-R55 [83]. TNF-R75/TNF-alpha complex may exhibit enhanced and/or specific intracellular function. Heterogeneity in the TNF-alpha response may also be caused by different postreceptor signal transduction pathways [75]. It is not clear, however, whether TNF-alpha receptor trimerization is necessary for activation, or whether receptor dimerization is sufficient, or if receptor trimerization triggers other and/or additional intracellular pathways.

Proteolytic cleavage of the extracellular domain of each TNF-R produces two soluble receptors, TNF-sR55 and TNF-sR75. OA synovial fibroblasts and chondrocytes release a significantly elevated level of TNF-sR75 [4,16]. A higher ratio of TNF-sR75/TNF-sR55 is noted in the more severe cases of arthritis [21,22,70]. At low concentrations, TNF-sR seems to stabilize the trimeric structure of TNF-alpha, thereby increasing the half-life of bioactive TNF-alpha [2], while at high concentrations, TNF-sR reduce the bioactivity of TNF-alpha by competing for TNF binding with cell-associated receptors [40]. How-

ever, as the affinity of both TNF-sR is similar to that of the plasma membrane receptor, large amounts of these inhibitors are required to decrease TNF-alpha activity.

The balance between cytokine-driven anabolic and catabolic processes determines the integrity of articular joint tissue. Other proinflammatory cytokines such as IL-6, IL-8, LIF, IL-11, and IL-17 have been shown to be expressed in OA tissue, and have therefore been considered potential contributing factors in the pathogenesis of this disease.

IL-6 has been proposed as a contributor to the OA pathological process by: (1) increasing the number of inflammatory cells in synovial tissue [35]; (2) stimulating the proliferation of chondrocytes; and (3) inducing an amplification of the IL-1 effects on the increased synthesis of metalloproteases (MMP) and inhibiting proteoglycan production [64]. However, as IL-6 can induce the production of TIMP [55], and not MMP, it is believed that this cytokine is involved in the feedback mechanism that limits proteolytic damage.

Interleukin-8 is a potent chemotactic cytokine for polymorphonuclear neutrophils (PMN), stimulating their chemotaxis and generating reactive oxygen metabolites [93]. This chemokine is synthesized by a variety of cells including monocytes/macrophages, chondrocytes and fibroblasts [41,49,50,86]. IL-8 plays an important role in the acute inflammatory reaction. In synovial culture, TNF-alpha stimulates the production of IL-8 in a time- and dose-dependent manner [41]. In OA patients, IL-beta, IL-6, TNF-alpha and IL-8 coexist in the synovial fluid. IL-8 enhances the release of IL-1beta, IL-6 and TNF-α [93]. The presence of IL-8 in the lining cell layers could explain the high amount of IL-8 in the synovial fluid [27]. IL-8 is also present in the chondrocytes, and has been shown to enhance the production of oxidative and 5-lipoxygenase products [74]. Stimulated human articular chondrocytes express the IL-8 gene and secrete bioactive IL-8 [57].

Leukemia inhibitory factor (LIF) is a single-chain glycoprotein that has diverse effects, including induction of acute-phase protein synthesis and the inhibition of lipoprotein lipase activity. LIF level has been detected in synovial fluid of OA patients [25]. LIF has been shown to enhance IL-1beta and IL-8 expression in chondrocytes, and IL-1beta and TNF-alpha in synovial fibroblasts [89]. IL-1beta and TNF-alpha upregulate LIF production [18,36,56]. LIF regulates the metabolism of connective tissue such as cartilage and bone [1,69], induces expression of collagenase and stromelysin but not tissue inhibitor of metalloproteases, TIMP [56]. This cytokine stimulates cartilage proteoglycan resorption [20] as well as nitric oxide (NO) production.

The IL-11 receptor shares the gp 130 domain with the LIF and IL-6 receptors, suggesting that they may have similar actions. This cytokine was originally identified as a stromal cell-derived lymphoietic and hematopoietic factor, but can also be induced in articular chondrocyte and synovial fibroblast cultures [58,65]. IL-11 has been found to decrease the release of PGE_2 from OA synovial fibroblasts [6], suggesting that IL-11 can prevent the excessive extracellular matrix degeneration induced by synovial inflammation.

IL-17 is a newly discovered cytokine of 20–30 kD present as a homodimer with variable glycosylated polypeptides [92]. The tissue distribution of IL-17R appears ubiquitous, and it is not yet known whether all cells expressing IL-17R respond to its ligand. IL-17 upregulates a number of gene products involved in cell activation, including the proinflammatory cytokines IL-1beta, TNF-alpha and IL-6, as well as MMP in target cells such as human macrophages [46]. IL-17 also increases the production of NO in chondrocyte cultures [9,60].

2.2. *Antiinflammatory cytokines*

Three antiinflammatory cytokines (IL-4, IL-10, and IL-13) are spontaneously elaborated by synovial membrane and cartilage, and are found in increased levels in the synovial fluid of OA patients. The antiinflammatory properties of these cytokines include decreased production of IL-1beta, TNF-alpha and MMP, upregulation of IL-1Ra and TIMP-1, and inhibition of PGE_2 release [5,30,31,38,39,47,78,88]. It was found that IL-10 modulated TNF-alpha production by increasing the release of the TNF-sR from monocytes in culture, while downregulating the receptor surface expression [38]. In human OA synovial fibroblasts, IL-10 also downregulated the TNF-R density, while increasing the release of TNF-alpha-induced TNF-Rs75. In these cells, however, IL-4 upregulated TNF-R, and enhanced TNF-alpha-induced TNF-sR75 [5]. In mononuclear cells from RA synovial fluid, both TNF-R55 and TNF-R75 are upregulated by IL-4 [23], and contrasts with data from monocytes, where this antiinflammatory cytokine downregulated both the membrane and soluble TNF-R [48].

IL-13 has been shown to have important biological activities such as inhibiting the production of a wide range of proinflammatory cytokines, while increasing IL-1Ra production [24,26]. In human synovial membrane specimens from OA patients treated with LPS, *in vitro* IL-13 inhibited the synthesis of IL-1beta, TNF-alpha and stromelysin, and increased production of IL-1Ra [47], but not in cells recovered from the synovial fluid of OA and RA patients [24]. The TNF receptor system does not appear to be a target for IL-13 in OA synovial fibroblasts [5].

IL-1Ra is a competitive inhibitor of IL-1R. This molecule does not bind to IL-1, is not a binding protein, nor does it stimulate target cells. IL-1Ra can block many of the effects observed during the pathological process of OA, including PGE_2 synthesis in synovial cells, collagenase production by chondrocytes, and cartilage matrix degradation. Three forms of IL-1Ra were found, one extracellular and termed soluble IL-1Ra (IL-1sRa), and two intracellular, icIL-1RaI and icIL-1RaII [8]. Both the soluble and icIL-1Ra can bind to IL-1R, but with about 5-fold less affinity for the latter. Although intensive research is underway, the biological actions of icIL-1Ra remain elusive. *In vitro* experiments have revealed that an excess of 10–100 times the amount of IL-1Ra is necessary to inhibit IL-1beta activity whereas, *in vivo*, 100–2000 times more IL-1Ra is needed [8,67]. This may likely explain why, even though a higher level of IL-1Ra is found in OA articular tissue, there is a relative deficit of IL-1Ra to IL-1beta in this tissue. This in turn may cause the increased level of IL-1beta activity.

3. Potential therapeutic applications of cytokine modulation in OA

The neutralization of IL-1 and/or TNF-α up-regulation of MMP gene expression appears to be a logical development in the potential medical therapy of OA. Indeed, recombinant IL-1 receptor antagonists (ILRa) and soluble IL-1 receptor proteins have been tested in both animal models of OA for modification of OA progression. Soluble IL-1Ra suppressed MMP-3 transcription in the rabbit synovial cell line HIG-82. Experimental evidence showing that neutralizing TNF-α suppressed cartilage degradation in arthritis also supports such strategy. The important role of TNF-α in OA may emerge from the fact that human articular chondrocytes from OA cartilage expressed a significantly higher number of the p55 TNF-alpha receptor that could make OA cartilage particularly susceptible to TNF-alpha degradative stimuli. In addition, OA cartilage produces more TNF-α and TNF-α convertase enzyme (TACE) mRNA than normal cartilage. By analogy, an inhibitor to the p55 TNF-α receptor may also provide a mechanism for abolishing TNF-α-induced degradation of cartilage ECM by MMPs. Since TACE is

the regulator of TNF-α activity, limiting the activity of TACE might also prove efficacious in OA. IL-1 and TNF-α inhibition of chondrocyte compensatory biosynthesis pathways which further compromise cartilage repair must also be dealt with, perhaps by employing stimulatory agents such as transforming growth factor-beta or insulin-like growth factor-I.

The capacity of IL-1Ra to reduce *in vitro* and *in vivo* cartilage degradation, MMP production and the progression of OA lesions [19,66] has elicited much attention concerning the use of this molecule in OA therapy, and more particularly in regard to gene therapy. Using the MFG retrovirus, the IL-1Ra gene has been successfully transferred into animal and human synovial cells using an *ex vivo* technique [10,32]. One such study using the experimental dog model of OA showed *in vivo* that the progression of structural changes of OA was significantly reduced [66]. It has also been demonstrated *in vitro* that the human IL-1Ra gene can be successfully transferred into chondrocytes using the Ad.RSV adenovirus, and that the resulting increase in production of IL-1Ra can protect the OA cartilage explants from degradation induced by IL-1 [10].

A novel and interesting approach to controlling proinflammatory cytokine production and/or activity is the use of biological molecules possessing antiinflammatory properties. Augmenting inhibitor production *in situ* by gene therapy or supplementing it by injecting the recombinant protein is an attractive therapeutic target, although an *in vivo* assay in OA is not available, and its applicability has yet to be proven. As such, recombinant human IL-4 (rhIL-4) has been tested *in vitro* on OA synovial tissue, and has been shown to suppress the synthesis of both IL-1beta and TNF-alpha in the same manner as low-dose dexamethasone [11]. To date, of the antiinflammatory cytokines, only IL-10 is employed in clinical trials for the treatment of RA in humans. Results from IL-13 experimentation on human synovial membrane from OA patients [47] indicate it is potentially useful in the treatment of this disease.

4. Conclusion

Although the primary etiology of OA remains undetermined, it is now believed that cartilage integrity is maintained by a balance obtained from cytokine-driven anabolic and catabolic processes. In OA, the specific causative for the pathological process has not been identified, but synovial inflammation at the clinical stage is now a well-documented phenomenon. An excess of proinflammatory cytokines is thought to be responsible for many clinical manifestations of OA. Other cytokines having anti-inflammatory properties could modulate this pathological process; therefore, these cytokines may prevent inflammation in OA.

In summary, modulation of cytokines that control MMP gene up-regulation would appear to be fertile targets for drug development in the treatment of OA. Several studies illustrate the potential importance of modulating IL-1 activity as a means to reduce the progression of the structural changes in OA. In the experimental dog and rabbit models of OA, we have demonstrated that *in vivo* intraarticular injections of the IL-Ra gene can prevent the progression of structural changes in OA. Future directions in the research and treatment of osteoarthritis (OA) will be based on the emerging picture of pathophysiological events that modulate the initiation and progression of OA.

References

[1] E. Abe, H. Tanaka, Y. Ishimi, C. Miyaura, T. Hayashi, H. Nagasawa, M. Tomida, Y. Yamaguchi, M. Hozumi and T. Suda, Differentiation-inducing factor purified from conditioned medium of mitogen-treated spleen cell cultures stimulates bone resorption, *Proc. Natl. Acad. Sci. USA* **83** (1986), 5958–5962.

[2] D. Aderka, H. Engelmann, Y. Maor, C. Brakebusch and D. Wallach, Stabilization of the bioactivity of tumor necrosis factor by its soluble receptors, *J. Exp. Med.* **175** (1992), 323–329.
[3] B.B. Aggarwal, W.J. Kohr, P.E. Hass, B. Moffat, S.A. Spencer, W.J. Henzel, T.S. Bringman, G.E. Nedwin, D.V. Goeddel and R.N. Harkins, Human tumor necrosis factor. Production, purification, and characterization, *J. Biol. Chem.* **260** (1985), 2345–2354.
[4] N. Alaaeddine, J.A. Di Battista, J.P. Pelletier, J.M. Cloutier, K. Kiansa, M. Dupuis and J. Martel-Pelletier, Osteoarthritic synovial fibroblasts possess an increased level of tumor necrosis factor-receptor 55 (TNF-R55) that mediates biological activation by TNF-alpha, *J. Rheumatol.* **24** (1997), 1985–1994.
[5] N. Alaaeddine, J.A. Di Battista, J.P. Pelletier, K. Kiansa, J.M. Cloutier and J. Martel-Pelletier, Inhibition of tumor necrosis factor alpha-induced prostaglandin E2 production by the antiinflammatory cytokines interleukin-4, interleukin-10, and interleukin-13 in osteoarthritic synovial fibroblasts: distinct targeting in the signaling pathways, *Arthritis Rheum.* **42** (1999), 710–718.
[6] N. Alaaeddine, J.A. Di Battista, J.P. Pelletier, K. Kiansa, J.M. Cloutier and J. Martel-Pelletier, Differential effects of IL-8, LIF (pro-inflammatory) and IL-11 (anti-inflammatory) on TNF-alpha-induced PGE_2 release and on signaling pathways in human OA synovial fibroblasts, *Cytokine* (1999) in press.
[7] A.R. Amin, Regulation of tumor necrosis factor-alpha and tumor necrosis factor converting enzyme in human osteoarthritis, *Osteoarthritis Cart.* **7** (1999), 392–394.
[8] W.P. Arend, Interleukin-1 receptor antagonist. [Review], *Adv. Immunol.* **54** (1993), 167–227.
[9] M.G. Attur, R.N. Patel, S.B. Abramson and A.R. Amin, Interleukin-17 up-regulation of nitric oxide production in human osteoarthritis cartilage, *Arthritis Rheum.* **40** (1997), 1050–1053.
[10] V.M. Baragi, R.R. Renkiewicz, H. Jordan, J. Bonadio, J.W. Harman and B.J. Roessler, Transplantation of transduced chondrocytes protects articular cartilage from interleukin 1-induced extracellular matrix degradation, *J. Clin. Invest.* **96** (1995), 2454–2460.
[11] A. Bendrups, A. Hilton, A. Meager and J.A. Hamilton, Reduction of tumor necrosis factor alpha and interleukin-1 beta levels in human synovial tissue by interleukin-4 and glucocorticoid, *Rheumatol. Int.* **12** (1993), 217–220.
[12] D.R. Bertolini, G.E. Nedwin, T.S. Bringman, D.D. Smith and G.R. Mundy, Stimulation of bone resorption and inhibition of bone formation *in vitro* by human tumour necrosis factors, *Nature* **319** (1986), 516–518.
[13] R.A. Black, S.R. Kronheim, M. Cantrell, M.C. Deeley, C.J. March, K.S. Prickett, J. Wignall, P.J. Conlon, D. Cosman, T.P. Hopp and D.Y. Mochizuki, Generation of biologically active interleukin-1 beta by proteolytic cleavage of the inactive precursor, *J. Biol. Chem.* **263** (1988), 9437–9442.
[14] R.A. Black, C.T. Rauch, C.J. Kozlosky, J.J. Peschon, J.L. Slack, M.F. Wolfson, B.J. Castner, K.L. Stocking, P. Reddy, S. Srinivasan, N. Nelson, N. Boiani, K.A. Schooley, M. Gerhart, R. Davis, J.N. Fitzner, R.S. Johnson, R.J. Paxton, C.J. March and D.P. Cerretti, A metalloproteinase disintegrin that releases tumour-necrosis factor-alpha from cells, *Nature* **385** (1997), 729–733.
[15] F.M. Brennan, D. Chantry, A. Jackson, R.N. Maini and M. Feldmann, Inhibitory effect of TNF alpha antibodies on synovial cell interleukin-1 production in rheumatoid arthritis, *Lancet* **2** (1989), 244–247.
[16] F.M. Brennan, D.L. Gibbons, A.P. Cope, P. Katsikis, R.N. Maini and M. Feldmann, TNF inhibitors are produced spontaneously by rheumatoid and osteoarthritic synovial joint cell cultures: evidence of feedback control of TNF action, *Scand. J. Immunol.* **42** (1995), 158–165.
[17] D. Camerini, G. Walz, W.A. Loenen, J. Borst and B. Seed, The T cell activation antigen CD27 is a member of the nerve growth factor/tumor necrosis factor receptor gene family, *J. Immunol.* **147** (1991), 3165–3169.
[18] I.K. Campbell, P. Waring, U. Novak and J.A. Hamilton, Production of leukemia inhibitory factor by human articular chondrocytes and cartilage in response to interleukin-1 and tumor necrosis factor alpha, *Arthritis Rheum.* **36** (1993), 790–794.
[19] J.P. Caron, J.C. Fernandes, J. Martel-Pelletier, G. Tardif, F. Mineau, C. Geng and J.P. Pelletier, Chondroprotective effect of intraarticular injections of interleukin-1 receptor antagonist in experimental osteoarthritis: suppression of collagenase-1 expression, *Arthritis Rheum.* **39** (1996), 1535–1544.
[20] G.J. Carroll and M.C. Bell, Leukaemia inhibitory factor stimulates proteoglycan resorption in porcine articular cartilage, *Rheumatol. Int.* **13** (1993), 5–8.
[21] I.C. Chikanza, P. Roux-Lombard, J.M. Dayer and G.S. Panayi, Tumour necrosis factor soluble receptors behave as acute phase reactants following surgery in patients with rheumatoid arthritis, chronic osteomyelitis and osteoarthritis, *Clin. Exp. Immunol.* **92** (1993), 19–22.
[22] A.P. Cope, D. Aderka, M. Doherty, H. Engelmann, D. Gibbons, A.C. Jones, F.M. Brennan, R.N. Maini, D. Wallach and M. Feldmann, Increased levels of soluble tumor necrosis factor receptors in the sera and synovial fluid of patients with rheumatic diseases, *Arthritis Rheum.* **35** (1992), 1160–1169.
[23] A.P. Cope, D.L. Gibbons, D. Aderka, B.M. Foxwell, D. Wallach, R.N. Maini, M. Feldmann and F.M. Brennan, Differential regulation of tumour necrosis factor receptors (TNF-R) by IL-4; upregulation of P55 and P75 TNF-R on synovial joint mononuclear cells, *Cytokine* **5** (1993), 205–212.

[24] R. de Waal Malefyt, C.G. Figdor, R. Huijbens, S. Mohan-Peterson, B. Bennett, J.A. Culpepper, W. Dang, G. Zurawski and J.E. de Vries, Effects of IL-13 on phenotype, cytokine production, and cytotoxic function of human monocytes. Comparison with IL-4 and modulation by IFN-gamma or IL-10, *J. Immunol.* **151** (1993), 6370–6381.
[25] J. Dechanet, J.L. Taupin, P. Chomarat, M.C. Rissoan, J.F. Moreau, J. Banchereau and P. Miossec, Interleukin-4 but not interleukin-10 inhibits the production of leukemia inhibitory factor by rheumatoid synovium and synoviocytes, *Eur. J. Immunol.* **24** (1994), 3222–3228.
[26] T. Defrance, P. Carayon, G. Billian, J.-C. Guillemot, A. Minty, D. Caput and P. Ferrara, Interleukin 13 is a B cell stimulating factor, *J. Exp. Med.* **179** (1994), 135–143.
[27] B. Deleuran, P. Lemche, M.S. Kristensen, C.Q. Chu, M. Field, J. Jensen, K. Matsushima and K. Stengaard-Pedersen, Localisation of interleukin 8 in the synovial membrane, cartilage-pannus junction and chondrocytes in rheumatoid arthritis, *Scand. J. Rheumatol.* **23** (1994), 2–7.
[28] W. Digel, W. Schoniger, M. Stefanic, H. Janssen, C. Buck, M. Schmid, A. Raghavachar and F. Porzsolt, Receptors for tumor necrosis factor on neoplastic B cells from chronic lymphocytic leukemia are expressed *in vitro* but not *in vivo*, *Blood* **76** (1990), 1607–1613.
[29] C.A. Dinarello, Biologic basis for interleukin-1 in disease, *Blood* **87** (1996), 2095–2147.
[30] R.P. Donnelly, M.J. Fenton, D.S. Finbloom and T.L. Gerrard, Differential regulation of IL-1 production in human monocytes by IFN-gamma and IL-4, *J. Immunol.* **145** (1990), 569–575.
[31] R. Essner, K. Rhoades, W.H. McBride, D.L. Morton and J.S. Economou, IL-4 down-regulates IL-1 and TNF gene expression in human monocytes, *J. Immunol.* **142** (1989), 3857–3861.
[32] C.H. Evans and P.D. Robbins, Gene therapy for arthritis, in: *Gene Therapeutics: Methods and Applications of Direct Gene Transfer*, J.A. Wolff, ed., Birkhauser, Boston, 1994, pp. 320–343.
[33] M.N. Farahat, G. Yanni, R. Poston and G.S. Panayi, Cytokine expression in synovial membranes of patients with rheumatoid arthritis and osteoarthritis, *Ann. Rheum. Dis.* **52** (1993), 870–875.
[34] M. Feldmann, F.M. Brennan and R.N. Maini, Role of cytokines in rheumatoid arthritis, *Annu. Rev. Immunol.* **14** (1996), 397–440.
[35] P.A. Guerne, B.L. Zuraw, J.H. Vaughan, D.A. Carson and M. Lotz, Synovium as a source as interleukin-6 *in vitro*: Contribution to local and systemic manifestations of arthritis, *J. Clin. Invest.* **83** (1989), 585–592.
[36] J.A. Hamilton, P.M. Waring and E.L. Filonzi, Induction of leukemia inhibitory factor in human synovial fibroblasts by IL-1 and tumor necrosis factor-alpha, *J. Immunol.* **150** (1993), 1496–1502.
[37] B. Haraoui, J.P. Pelletier, J.M. Cloutier, M.P. Faure and J. Martel-Pelletier, Synovial membrane histology and immunopathology in rheumatoid arthritis and osteoarthritis, *In vivo* effects of anti-rheumatic drugs, *Arthritis Rheum.* **34** (1991), 153–163.
[38] P.H. Hart, M.J. Ahern, M.D. Smith and J.J. Finlay-Jones, Comparison of the suppressive effects of interleukin-10 and interleukin-4 on synovial fluid macrophages and blood monocytes from patients with inflammatory arthritis, *Immunology* **84** (1995), 536–542.
[39] P.H. Hart, G.F. Vitti, D.R. Burgess, G.A. Whitty, D.S. Piccoli and J.A. Hamilton, Potential antiinflammatory effects of interleukin 4: suppression of human monocyte tumor necrosis factor alpha, interleukin 1, and prostaglandin E_2, *Proc. Natl. Acad. Sci. USA* **86** (1989), 3803–3807.
[40] M. Higuchi and B.B. Aggarwal, Inhibition of ligand binding and antiproliferative effects of tumor necrosis factor and lymphotoxin by soluble forms of recombinant P60 and P80 receptors, *Biochem. Biophys. Res. Commun.* **182** (1992), 638–643.
[41] K. Hirota, T. Akahoshi, H. Endo, H. Kondo and S. Kashiwazaki, Production of interleukin 8 by cultured synovial cells in response to interleukin 1 and tumor necrosis factor, *Rheumatol. Int.* **12** (1992), 13–16.
[42] H.P. Hohmann, M. Brockhaus, P.A. Baeuerle, R. Remy, R. Kolbeck and A.P. van Loon, Expression of the types A and B tumor necrosis factor (TNF) receptors is independently regulated, and both receptors mediate activation of the transcription factor NF-kappa B. TNF alpha is not needed for induction of a biological effect via TNF receptors, *J. Biol. Chem.* **265** (1990), 22 409–22 417.
[43] A.J. Hough, Pathology of osteoarthritis, in: *Arthritis and Allied Conditions*, W.J. Koopman, ed., Williams and Wilkins, Baltimore, 1997, pp. 1945–1968.
[44] O.M. Howard, K.A. Clouse, C. Smith, R.G. Goodwin and W.L. Farrar, Soluble tumor necrosis factor receptor: inhibition of human immunodeficiency virus activation, *Proc. Natl. Acad. Sci. USA* **90** (1993), 2335–2339.
[45] N. Itoh, S. Yonehara, A. Ishii, M. Yonehara, S. Mizushima, M. Sameshima, A. Hase, Y. Seto and S. Nagata, The polypeptide encoded by the cDNA for human cell surface antigen Fas can mediate apoptosis, *Cell* **66** (1991), 233–243.
[46] D. Jovanovic, J.A. Di Battista, J. Martel-Pelletier, F.C. Jolicoeur, Y. He, M. Zhang, F. Mineau and J.P. Pelletier, Interleukin-17 (IL-17) stimulates the production and expression of proinflammatory cytokines, IL-beta and TNF-alpha, by human macrophages, *J. Immunol.* **160** (1998), 3513–3521.
[47] D. Jovanovic, J.P. Pelletier, N. Alaaeddine, F. Mineau, C. Geng, P. Ranger and J. Martel-Pelletier, Effect of IL-13 on cytokines, cytokine receptors and inhibitors on human osteoarthritic synovium and synovial fibroblasts, *Osteoarthritis*

Cart. **6** (1998), 40–49.
[48] D.A. Joyce, D.P. Gibbons, P. Green, J.H. Steer, M. Feldmann and F.M. Brennan, Two inhibitors of pro-inflammatory cytokine release, interleukin-10 and interleukin-4, have contrasting effects on release of soluble p75 tumor necrosis factor receptor by cultured monocytes, *Eur. J. Immunol.* **24** (1994), 2699–2705.
[49] A.E. Koch, S.L. Kunkel, J.C. Burrows, H.L. Evanoff, G.K. Haines, R.M. Pope and R.M. Strieter, Synovial tissue macrophage as a source of the chemotactic cytokine IL-8, *J. Immunol.* **147** (1991), 2187–2195.
[50] M.S. Kristensen, K. Paludan, C.G. Larsen, C.O. Zachariae, B.W. Deleuran, P.K. Jensen, P. Jorgensen and K. Thestrup-Pedersen, Quantitative determination of IL-1 alpha-induced IL-8 mRNA levels in cultured human keratinocytes, dermal fibroblasts, endothelial cells, and monocytes, *J. Invest. Dermatol.* **97** (1991), 506–510.
[51] S.R. Kronheim, A. Mumma, T. Greenstreet, P.J. Glackin, K. Van Ness, C.J. March and R.A. Black, Purification of interleukin-1 beta converting enzyme, the protease that cleaves the interleukin-1 beta precursor, *Arch. Biochem. Biophys.* **296** (1992), 698–703.
[52] M. Lewis, L.A. Tartaglia, A. Lee, G.L. Bennett, G.C. Rice, G.H. Wong, E.Y. Chen and D.V. Goeddel, Cloning and expression of cDNAs for two distinct murine tumor necrosis factor receptors demonstrate one receptor is species specific, *Proc. Natl. Acad. Sci. USA* **88** (1991), 2830–2834.
[53] S. Lindblad and E. Hedfors, Arthroscopic and immunohistologic characterization of knee joint synovitis in osteoarthritis, *Arthritis Rheum.* **30** (1987), 1081–1088.
[54] H. Loetscher, Y.C.E. Pan, H.W. Lahm, R. Gentz, M. Brockhaus, H. Tabuchi and W. Lesslauer, Molecular cloning and expression of the human 55 kd tumor necrosis factor receptor, *Cell* **61** (1990), 351–359.
[55] M. Lotz and P.A. Guerne, Interleukin-6 induces the synthesis of tissue inhibitor of metalloproteinases-1/erythroid potentiating activity, *J. Biol. Chem.* **266** (1991), 2017–2020.
[56] M. Lotz, T. Moats and P.M. Villiger, Leukemia inhibitory factor is expressed in cartilage and synovium and can contribute to the pathogenesis of arthritis, *J. Clin. Invest.* **90** (1992), 888-896.
[57] M. Lotz, R. Terkeltaub and P.M. Villiger, Cartilage and joint inflammation. Regulation of IL-8 expression by human articular chondrocytes, *J. Immunol.* **148** (1992), 466–473.
[58] R. Maier, V. Ganu and M. Lotz, Interleukin-11, an inducible cytokine in human articular chondrocytes and synoviocytes, stimulates the production of the tissue inhibitor of metalloproteinases, *J. Biol. Chem.* **268** (1993), 21 527–21 532.
[59] J. Martel-Pelletier, R. McCollum, J.A. Di Battista, M.P. Faure, J.A. Chin, S. Fournier, M. Sarfati and J.P. Pelletier, The interleukin-1 receptor in normal and osteoarthritic human articular chondrocytes. Identification as the type I receptor and analysis of binding kinetics and biologic function, *Arthritis Rheum.* **35** (1992), 530–540.
[60] J. Martel-Pelletier, F. Mineau, D. Jovanovic, J.A. Di Battista and J.P. Pelletier, MAPK and NF-B together regulate the IL-17-induced nitric oxide production in human OA chondrocytes: possible role of transactivating factor MAPKAP-K, *Arthritis Rheum.* (1999) (in press).
[61] B. Mosley, D.L. Urdal, K.S. Prickett, A. Larsen, D. Cosman, P.J. Conlon, S. Gillis and S.K. Dower, The interleukin-1 receptor binds the human interleukin-1 alpha precursor but not the interleukin-1 beta precursor, *J. Biol. Chem.* **262** (1987), 2941–2944.
[62] S.L. Myers, K.D. Brandt, J.W. Ehlich, E.M. Braunstein, K.D. Shelbourne, D.A. Heck and L.A. Kalasinski, Synovial inflammation in patients with early osteoarthritis of the knee, *J. Rheumatol.* **17** (1990), 1662–1669.
[63] B. Naume, R. Shalaby, W. Lesslauer and T. Espevik, Involvement of the 55- and 75-kDa tumor necrosis factor receptors in the generation of lymphokine-activated killer cell activity and proliferation of natural killer cells, *J. Immunol.* **146** (1991), 3045–3048.
[64] J.J. Nietfeld, B. Wilbrink, M. Helle, J.L. van Roy, W. den Otter, A.J. Swaak and O. Huber-Bruning, Interleukin-1-induced interleukin-6 is required for the inhibition of proteoglycan synthesis by interleukin-1 in human articular cartilage, *Arthritis Rheum.* **33** (1990), 1695–1701.
[65] S.R. Paul, F. Bennett, J.A. Calvetti, K. Kelleher, C.R. Wood, R.M.Jr. O'Hara, A.C. Leary, B. Sibley, S.C. Clark and D.A. Williams, Molecular cloning of a cDNA encoding interleukin 11, a stromal cell-derived lymphopoietic and hematopoietic cytokine, *Proc. Natl. Acad. Sci. USA* **87** (1990), 7512–7516.
[66] J.P. Pelletier, J.P. Caron, C.H. Evans, P.D. Robbins, H.I. Georgescu, D. Jovanovic, J.C. Fernandes and J. Martel-Pelletier, *In vivo* suppression of early experimental osteoarthritis by IL-Ra using gene therapy, *Arthritis Rheum.* **40** (1997), 1012–1019.
[67] J.P. Pelletier, R. McCollum, J.M. Cloutier and J. Martel-Pelletier, Synthesis of metalloproteases and interleukin 6 (IL-6) in human osteoarthritic synovial membrane is an IL-1 mediated process, *J. Rheumatol.* **22** (1995), 109–114.
[68] D. Plows, L. Probert, S. Georgopoulos, L. Alexopoulou and G. Kollias, The role of tumour necrosis factor (TNF) in arthritis: studies in transgenic mice, *Rheumatol. Eur.* (Suppl. 2) (1995), 51–54.
[69] L.R. Reid, C. Lowe, J. Cornish, S.J. Skinner, D.J. Hilton, T.A. Willson, D.P. Gearing and T.J. Martin, Leukemia inhibitory factor: a novel bone-active cytokine, *Endocrinology* **126** (1990), 1416–1420.
[70] P. Roux-Lombard, L. Punzi, F. Hasler, S. Bas, S. Todesco, H. Gallati, P.A. Guerne and J.M. Dayer, Soluble tumor necrosis factor receptors in human inflammatory synovial fluids, *Arthritis Rheum.* **36** (1993), 485–489.

[71] M. Sadouk, J.P. Pelletier, G. Tardif, K. Kiansa, J.M. Cloutier and J. Martel-Pelletier, Human synovial fibroblasts coexpress interleukin-1 receptor type I and type II mRNA: The increased level of the interleukin-1 receptor in osteoarthritic cells is related to an increased level of the type I receptor, *Lab. Invest.* **73** (1995), 347–355.
[72] T.J. Schall, M. Lewis, K.J. Koller, A. Lee, G.C. Rice, G.H. Wong, T. Gatanaga, G.A. Granger, R. Lentz and H. Raab, Molecular cloning and expression of a receptor for human tumor necrosis factor, *Cell* **61** (1990), 361–370.
[73] P. Scheurich, B. Thoma, U. Ucer and K. Pfizenmaier, Immunoregulatory activity of recombinant human tumor necrosis factor (TNF)-alpha: induction of TNF receptors on human T cells and TNF-alpha-mediated enhancement of T cell responses, *J. Immunol.* **138** (1987), 1786–1790.
[74] J.M. Schroder, The monocyte-derived neutrophil activating peptide (NAP/interleukin 8) stimulates human neutrophil arachidonate-5-lipoxygenase, but not the release of cellular arachidonate, *J. Exp. Med.* **170** (1989), 847–863.
[75] S. Schutze, K. Potthoff, T. Machleidt, D. Berkovic, K. Wiegmann and M. Kronke, TNF activates NF-kappa B by phosphatidylcholine-specific phospholipase C-induced "acidic" sphingomyelin breakdown, *Cell* **71** (1992), 765–776.
[76] M.R. Shalaby, M.A.Jr. Palladino, S.E. Hirabayashi, T.E. Eessalu, G.D. Lewis, H.M. Shepard and B.B. Aggarwal, Receptor binding and activation of polymorphonuclear neutrophils by tumor necrosis factor-alpha, *J. Leukoc. Biol.* **41** (1987), 196–204.
[77] M.R. Shalaby, A. Sundan, H. Loetscher, M. Brockhaus, W. Lesslauer and T. Espevik, Binding and regulation of cellular functions by monoclonal antibodies against human tumor necrosis factor receptors, *J. Exp. Med.* **172** (1990), 1517–1520.
[78] M. Shingu, S. Miyauchi, Y. Nagai, C. Yasutake and K. Horie, The role of IL-4 and IL-6 in IL-1-dependent cartilage matrix degradation, *Br. J. Rheumatol.* **34** (1995), 101–106.
[79] W.M. Siders, J.C. Klimovitz and S.B. Mizel, Characterization of the structural requirements and cell type specificity of IL-1 and IL-1 secretion, *J. Biol. Chem.* **268** (1993), 22 170–22 174.
[80] J. Slack, C.J. McMahan, S. Waugh, K. Schooley, M.K. Spriggs, J.E. Sims and S.K. Dower, Independent binding of interleukin-1 alpha and interleukin-1 beta to type I and type II interleukin-1 receptors, *J. Biol. Chem.* **268** (1993), 2513–2524.
[81] C.A. Smith, T. Davis, D. Anderson, L. Solam, M.P. Beckmann, R. Jerzy, S.K. Dower, D. Cosman and R.G. Goodwin, A receptor for tumor necrosis factor defines an unusual familx of cellular and viral proteins, *Science* **248** (1990), 1019–1023.
[82] M. Svenson, M.B. Hansen, P. Heegaard, K. Abell and K. Bendtzen, Specific binding of interleukin-1 (IL-1)- and IL-1 receptor antagonist (IL-1ra) to human serum. High-affinity binding of IL-1ra to soluble IL-1 receptor type I, *Cytokine* **5** (1993), 427–435.
[83] L.A. Tartaglia, D. Pennica and D.V. Goeddel, Ligand passing: the 75-kDa tumor necrosis factor (TNF) receptor recruits TNF for signaling by the 55-kDa TNF receptor, *J. Biol. Chem.* **268** (1993), 18 542–18 548.
[84] L.A. Tartaglia, R.F. Weber, I.S. Figari, C. Reynolds, M.A.Jr. Palladino and D.V. Goeddel, The two different receptors for tumor necrosis factor mediate distinct cellular responses, *Proc. Natl. Acad. Sci. USA* **88** (1991), 9292–9296.
[85] B. Thoma, M. Grell, K. Pfizenmaier and P. Scheurich, Identification of a 60-kD tumor necrosis factor (TNF) receptor as the major signal transducing component in TNF responses, *J. Exp. Med.* **172** (1990), 1019–1023.
[86] J. Van Damme, R.A. Bunning, R. Conings, R. Graham, G. Russell and G. Opdenakker, Characterization of granulocyte chemotactic activity from human cytokine-stimulated chondrocytes as interleukin 8, *Cytokine* **2** (1990), 106–111.
[87] F.A.J. Van de Loo, L.A. Joosten, P.L. van Lent, O.J. Arntz and W.B. van den Berg, Role of interleukin-1, tumor necrosis factor alpha, and interleukin-6 in cartilage proteoglycan metabolism and destruction. Effect of *in situ* blocking in murine antigen- and zymosan-induced arthritis, *Arthritis Rheum.* **38** (1995), 164–172.
[88] E. Vannier, L.C. Miller and C.A. Dinarello, Coordinated antiinflammatory effects of interleukin 4: interleukin 4 suppresses interleukin 1 production but up-regulates gene expression and synthesis of interleukin 1 receptor antagonist, *Proc. Natl. Acad. Sci. USA* **89** (1992), 4076–4080.
[89] P.M. Villiger, Y. Geng and M. Lotz, Induction of cytokine expression by leukemia inhibitory factor, *J. Clin. Invest.* **91** (1993), 1575–1581.
[90] C.I. Westacott, R.M. Atkins, P.A. Dieppe and C.J. Elson, Tumour necrosis factor-alpha receptor expression on chondrocytes isolated from human articular cartilage, *J. Rheumatol.* **21** (1994), 1710–1715.
[91] K.P. Wilson, J.A. Black, J.A. Thomson, E.E. Kim, J.P. Griffith, M.A. Navia, M.A. Murcko, S.P. Chambers, R.A. Aldape and S.A. Raybuck, Structure and mechanism of interleukin-1 beta converting enzyme, *Nature* **370** (1994), 270–275.
[92] Z. Yao, S.L. Painter, W.C. Fanslow, D. Ulrich, B.M. Macduff, M.K. Spriggs and R.J. Armitage, Human IL-17: a novel cytokine derived from T cells, *J. Immunol.* **155** (1995), 5483–5486.
[93] C.L. Yu, K.H. Sun, S.C. Shei, C.Y. Tsai, S.T. Tsai, J.C. Wang, T.S. Liao, W.M. Lin, H.L. Chen, H.S. Yu and S.H. Han, Interleukin 8 modulates interleukin-1 beta, interleukin-6 and tumor necrosis factor-alpha release from normal human mononuclear cells, *Immunopharmacology* **27** (1994), 207–214.